and GenBank accession no. Q96PY6; as **Exhibit C**, the result of a nucleic acid BLAST of SEQ ID NO:3 versus human genomic sequence.

RESPONSE

I. Status of the Claims

Claims 4, 5, and 11-14 are presently pending in the case.

II. Rejection of Claims Under 35 U.S.C. § 101

The Action continues to reject claims 4, 5 and 11-14 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by a specific, substantial, and credible utility or, in the alternative, a well-established utility. Applicants respectfully persist in their traverse.

The Action disagrees with Applicants' logical assertion, based on the evidence that essentially the same protein was identified by those of skill in the art in no way associated with Applicant indicates that Applicants assertions are credible. Given the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable, this is clear evidence that those skilled in the art would have recognized the function and activity of the protein encoded by the sequences of the present invention, there can, therefore, be no question that Applicants' asserted utility for the described sequences is "credible." According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

The Action fails to recognize Applicant's assertion that the present invention is a human kinase, in particular a variant of human NEK-1. This assertion is clearly credible and was supported by the evidence provided in Exhibits C-E submitted with Applicants previous response (Paper No. 13) Perhaps this confusion occurred because the Examiner is unfamiliar with the International Protein Index, a publically available database (http://srs.ebi.ac.uk/srs7bin/cgi-bin/wgetz?-page+LibInfo+-id+1DI5g1L3fHi+-lib+IPI). To further

clarify Applicant's assertions, enclosed the results of two amino acid sequence comparisons as exhibits. An amino acid sequence comparison between SEQ ID NO:4 of the present invention and accession number IPI00044749.2 is presented in **Exhibit A**. An amino acid sequence comparison between SEQ ID NO:4 of the present invention and GenBank (Swissprot) accession no. Q96PY6 is presented in **Exhibit B**. The results of both of these comparisons clearly show identity between the sequences of the present invention and those annotated by others, in no way associated with Applicants, as encoding *Homo sapiens* (Human) SERINE/THREONINE KINASE NEK-1 and Serine/threonine-protein kinase NEK1 (NimA-related protein kinase), respectively. The sequences of the present invention encode a human kinase, a shorter isoform of NEK-1.

In the face of such clearly persuasive evidence the Action discounts the value of the evidence provided in Applicants' previous response, as well as that given above. The Action argues that this evidence is without value because sequence homology identity is not persuasive because the relevant literature acknowledges that function cannot be based solely on structural similarity to a protein found in the sequence database. The Action then goes on to present what it considers to be a series of examples of such literature.

The Action cites Bork (Genome Research *10*:398-400, 2000) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The Action directs attention to page 399, on which the author notes the limitations of various methods of analysis. It is of interest that in his "analysis" Bork often uses citations to many of his own previous publications, an interesting approach. 'My position is supported by my previous disclosures of my position.' If Bork's position is supported by others of skill in the art, one would expect that he would reference them rather than himself to provide support for his statements. Given that the standard with regard to obtaining U.S. patents is those of skill in the art, this observation casts doubt on the broad applicability of Bork's position. It should also be noted that in Table 1, on page 399, in which selected examples of prediction accuracy are presented, that the reported accuracy of the methods which Applicants have employed are, in fact, very high. While nowhere in Bork is there a comparison of the prediction accuracy based on the percentage homology between two proteins or two classes of proteins, " Homology (several methods)" is assigned an accuracy rate of 98% and "Functional features by homology" is assigned an accuracy rate of 90%. Given that these figures were obtained based on what

is at least a 4 year old analysis, these high levels of accuracy would appear to support rather than refute Applicants assertions in the present case. Additionally Bork even states (on page 400, second column, line 17) that " However, there is still no doubt that sequence analysis is extremely powerful". In summary, it is clear that it is not Bork's intention to refute the value of sequence analysis but rather he is indicating that there is room for improvement.

The Action also cites Broun *et al.* (Science *282*:1315-1317, 1998) and Van de Loo *et al.* (Proc. Natl. Acad. Sci. USA *92*:6743-6747, 1995) as teaching that prediction of function based on homology is unpredictable. However, these papers cite only <u>one</u> example, microsomal oleate desaturase/oleate 12-hydroxylase, where function based on sequence homology proved to be incorrect. One example out of the thousands of predictions of function based on homology that exist in the art is hardly indicative of a high level of uncertainty, and thus also does not support the alleged lack of utility.

In summary a careful reading of the cited "relevant literature" does not in fact support the concept that function cannot be based on sequence and structural similarity, in contrast many of the examples actually support the use of such methodologies while identifying several areas in which caution should be exercised. These inaccuracies and potential pitfalls can be overcome by a more careful analysis by those of skill in the art. Automatic methods of sequence homology identification was only the staring point for consideration the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (2 experienced B.S. and 3 Ph.D. level scientists).

The Action also discounts Applicants' assertion regarding the use of the presently claimed polynucleotides on DNA chips, based on the position that such a use would allegedly be generic. Further, the Action seems to be requiring Applicants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of § 101. Applicants respectfully point out that knowledge of the exact function or role of the presently claimed sequence **<u>is not required</u>** to track expression patterns using a DNA chip. As set forth in Applicants First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences

would have great utility in such DNA chip applications. The claimed sequence provides a specific marker of the human genome (see evidence below), and that such specific markers are targets for discovering drugs that are associated with human disease. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details at least on page 9. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, as well as more recently issued U.S. Patent Nos. 5,837,832, 6,156,501 and 6,261,776. Accordingly, the present sequence has a specific utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequence, must also be useful.

Additionally, since only a small percentage of the genome (2-4%) actually encodes exons, which in-turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications, further discounting the Examiner's position that such uses are "generic". Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value that it was acquired by large pharmaceutical company, Merck & Co., for substantial sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human

genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

Further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the utility the present nucleotide sequence has a specific utility in determining the genomic structure of the corresponding human chromosome, for example mapping the protein encoding regions, as described in the specification and evidenced below. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences (see evidence below). In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the

practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

As still further evidence supporting Applicants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided in **Exhibit C**. This is the result of a blast analysis using SEQ ID NO:3 of the present invention when compared to the identified human genomic sequence. This result indicates that the sequence of the present invention is encoded by 31 exons spread non-contiguously along a region of human chromosome 4, which is represented by 5 adjacent BAC clones, AC116621,AC084724, AC116615, AC11643 and AC11642. Thus clearly one would not simply be able to identify the 31 protein encoding exons that make up the sequence of the present intention, nor to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what those specific sequences were. Additionally, it should be noted that the human NEK-1 kinase gene also maps to the same region of human chromosome 4 (4q32.3). This further supports Applicant's position that the sequences of the present invention encodes a variant of the human NEK-1 kinase.

Finally, the Action also argues, that Applicants' argument of due process presented in the previous response (Paper No. 13) is not persuasive. Applicants' understanding is that issued United States patents retain a legal presumption of validity which in this case indicates that the inventions claimed in the cited patents are *legally presumed* to be in full compliance with the provisions of 35 U.S.C. sections 101, 102, 103, and 112. Applicants respectfully submit that, absent a change in the law as enacted by Congress and signed by the President, it is improper for the Examiner to hold Applicants' invention to a different legal standard of patentability. Given the rapid pace of development in the biotechnology arts, it is difficult for the Applicants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could somehow retain *less* utility and

be *less* enabled than inventions in the cited issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, Applicants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record. Any argument to the contrary is at best arbitrary and at worst capricious. Absent authority provided by an act of Congress or Executive order, arbitrary or capricious conduct by an administrative office the U.S. government has historically proven to conflict with the provisions of the U.S. Constitution. The Patent Office does not have the authority to rewrite U.S. law. However, the Patent Office does have a Constitutional obligation to administer U.S. law in an unbiased and procedurally consistent manner. That is what the Applicants are respectfully requesting the Examiner to consider in the present matter.

For each of the foregoing reasons, Applicants submit that in light of the above discussion and those presented in Paper No. 13, the presently claimed invention has been shown to have a substantial, specific, credible and well-established utility and that the rejection of pending claims 4,5 and 11-14 under 35 U.S.C. § 101 has been avoided, and respectfully request that the rejection be withdrawn.

III. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 4,5 an 11-14 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the claimed invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 4,5 an 11-14 have been shown to have a specific, substantial, credible and well established utility, as detailed in section above. Applicants therefore respectfully request that the rejection of claims claims 4,5 an 11-14 under 35 U.S.C. § 112, first paragraph, be withdrawn.

V. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing amendments and remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Ramirez have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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